Enhanced responsiveness of GhsrQ343X rats to ghrelin results in enhanced adiposity without increased appetite

Yacine Chebani,1* Candice Marion,1* Philippe Zizzari,1* Khadidja Chettab,1 Marie Pastor,1 Marie Korostelev,1 David Geny,1 Jacques Epelbaum,1,2 Virginie Tolle,1 Séverine Morisset-Lopez,3 Jacques Pantel1,4†

Abstract

The ability of the gut hormone ghrelin to promote positive energy balance is mediated by the growth hormone secretagogue receptor (GHSR). GHSR is a G protein–coupled receptor (GPCR) that is found centrally and peripherally and that can signal in a ligand-independent manner basally or when heterodimerized with other GPCRs. However, current Ghsr knockout models cannot dissect ghrelin-dependent and ghrelin-independent signaling, precluding assessment of the physiological importance of these signaling pathways. An animal model carrying a Ghsr mutation that preserves GHSR cell surface abundance, but selectively alters GHSR signaling, would be a useful tool to decipher GHSR signaling in vivo. We used rats with the GhsrQ343X mutation (GhsrM/M), which is predicted to delete the distal part of the GHSR carboxyl-terminal tail, a domain critical for the signal termination processes of receptor internalization and β-arrestin recruitment. In cells, the GHSR-Q343X mutant showed enhanced ligand-induced G protein–dependent signaling and blunted activity of processes involved in GPCR signal termination. GhsrM/M rats displayed enhanced responses to submaximal doses of ghrelin or GHSR agonist. Moreover, GhsrM/M rats had a more stable body weight under caloric restriction, a condition that increases endogenous ghrelin tone, whereas under standard housing conditions, GhsrM/M rats showed increased body weight and adiposity and reduced glucose tolerance. Overall, our data stress the physiological role of the distal domain of GHSR carboxyl terminus as a suppressor of ghrelin sensitivity, and we propose using the GhsrM/M rat as a physiological model of gain of function in Ghsr to identify treatments for obesity-related conditions.